

Peptic Ulcer Disease and the *H. pylori* Bacterium: Treatment Regimens

GI Series, P4

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Part I. Introduction

Since the discovery of the *Helicobacter pylori* bacterium in 1983, researchers have identified the presence of this bacterium in many gastrointestinal diseases.¹ *H. pylori* is recognized as the most common cause of chronic active gastritis apparent in most cases of duodenal and gastric ulcer.² Other diseases associated with *H. pylori* include gastric cancer, gastric mucosal-associated lymphoid tissue (MALT) lymphoma, and possibly non-ulcer dyspepsia.³ Eradication of this organism therefore offers significant benefit for infected patients as well as health care resources. However, determining the best eradication therapy has been met with many challenges. Several treatment regimens have been studied with varying degrees of success.

Previous articles in this series have provided the reader with a general overview of *H. pylori* related disease states, appropriate guidelines for testing, and a description of the tests available for *H. pylori* detection. Diagnostic testing guidelines have been developed to identify those individuals most at risk for *H. pylori* infection. This includes patients with active peptic ulcer disease, documented past history of peptic ulcer disease, gastric MALT lymphoma, and a fear or family history of gastric ade-

The Department of Health and Hospitals, Bureau of Health Services Financing, and the University of Louisiana at Monroe, School of Pharmacy, continue to develop Disease Management programs to address the educational component of the Louisiana Medicaid Pharmacy Benefits Management system.

Selected Medicaid recipients and their health care practitioners receive these educational brochures. We appreciate your taking time to review these and incorporating this information into your practice as you deem appropriate.

Thank you for your continued participation in the Medicaid program. Should you need additional information concerning the Disease Management program, please contact M.J. Terrebonne at (225)342-9768.

nocarcinoma.⁴⁻⁵ Patients with non-ulcer dyspepsia should be evaluated based upon age, symptoms, and lifestyle to determine risk for infection and if testing is indicated.⁴⁻⁵ Finally, testing should be performed only if treatment is intended for those with a positive result.⁴⁻⁵

A 3-step approach is now becoming widely accepted in the management of *H. pylori* infection. This involves diagnosis, treatment, and confirmation of eradication. Testing for *H. pylori* is required for the first and last steps of the 3-step management. Testing can be performed either with non-invasive tests such as serology, breath tests, and stool antigen tests or by invasive endoscopy which allows the clinician to view histology samples, perform rapid urease tests, or culture the organism. The non-invasive tests are less expensive methods for detecting *H. pylori* when compared to those performed during endoscopy. However endoscopy allows for direct visualization of the mucosa, which may be necessary to obtain a definitive diagnosis. Serology tests, which are the least expensive have been found to have the lowest accuracy of the non-invasive tests for initial diagnosis and are not recommended for confirmation of eradication because the antigen tested may remain in the blood pool for many months after eradication.⁶ Breath tests and stool antigen tests can be used with confidence for initial diagnosis and confirmation of eradication. To achieve eradication of *H. pylori*, appropriate antibiotic treatment plus agents to help control symptoms and speed ulcer healing are necessary. This article will focus on recommended treatment regimens, the respective eradication rates, and factors that can influence the eradication rate.

Therapy for *H. pylori* Infection

Currently no therapy for *H. pylori* infection is 100% effective; however, several regimens have been studied and found to achieve acceptable cure rates of greater than 90%. An acceptable cure rate can be obtained with recommended triple or quadruple regimens which have durations of therapy from 7 to 14 days. The Food and Drug Administration has approved various medication regimens for treatment of *H. pylori* (Table 1).⁷

Dual Therapy

Some of the first treatment regimens used to treat *H. pylori* infection consisted of two drugs. Despite dual therapy being simple and often well tolerated, the eradication rate for dual therapy is generally lower than other suggested *H. pylori* treatment regimens. When evaluating treatment options for *H. pylori*, it is important to consider eradication rates along with other patient-specific factors.

Amoxicillin plus a Proton Pump Inhibitor. *H. pylori* is highly sensitive to amoxicillin. When administered orally, amoxicillin has a topical effect on gastric mucosa as well as a systemic effect of being secreted into the gastric juice from the blood stream.⁸ However by itself, amoxicillin results in eradication rates of less than 20% even in high doses of more than 2 grams per day.⁹ Significant increases in eradication rates occur when amoxicillin is administered in combination with a proton pump inhibitor (PPI) such as lansoprazole. The addition of the PPI is believed to decrease gastric secretions allowing intragastric amoxicillin concentrations to increase as well as increasing gastric

pH thus improving the efficacy of amoxicillin.¹⁰ The overall eradication rate for amoxicillin plus a PPI is still a disappointing 60% independent of dose and duration of therapy.¹¹ The FDA has restricted this dual therapy to be used only for patients who are allergic or intolerant to clarithromycin and for patients known or suspected to be infected with clarithromycin-resistant strains. *H. pylori* does not appear to develop resistance to amoxicillin, therefore, it can be utilized in subsequent therapy for cases of treatment failure.⁹

Clarithromycin plus a Proton Pump Inhibitor. Clarithromycin is a new generation macrolide antibiotic that is highly effective against *H. pylori*. Clarithromycin as a single agent has the highest eradication rates of any antibiotic used as monotherapy achieving eradication rates of 40% to 60%.¹² When used in combination with a PPI, such as omeprazole, eradication rates have been shown to rise 83%.¹³ The recommended therapy is clarithromycin 500mg three times a day with 40mg of omeprazole daily for 2 weeks then 20mg of omeprazole daily for another 2 weeks. Studies have shown that reduction in the dose of either clarithromycin or the PPI will cause a significant decrease in eradication rates. Disadvantages of clarithromycin are that resistance commonly will develop and side effects such as alterations in taste may cause patients to be noncompliant, both of which will negatively affect cure rates.

Table 1: FDA-Approved Treatment Options

Amoxicillin 1 g TID + lansoprazole 30 mg TID for 14 days*
Clarithromycin 500 mg TID + omeprazole 40 mg QD for 14 days, for patients with an active ulcer, an additional 14 days of omeprazole 20 mg QD is recommended
Amoxicillin 1 g BID + clarithromycin 500 mg BID + esomeprazole 40 mg QD for 10 days
Amoxicillin 1 g BID + clarithromycin 500 mg BID + lansoprazole 30 mg BID for 10 days or 14 days
Amoxicillin 1 g BID + clarithromycin 500 mg BID + omeprazole 20 mg BID for 10 days (If ulcer is present at time of initiation of therapy, an additional 18 days of omeprazole 20 mg QD is recommended for ulcer healing and symptom relief.)
Amoxicillin 1 g BID + clarithromycin 500 mg BID + rabeprazole 20 mg BID for 7 days
Tetracycline 500 mg QID + metronidazole 250 mg QID + bismuth subsalicylate 525 mg QID + H2-blocker therapy (as directed) for 14 days, then continue H2-blocker therapy as directed for an additional 2 to 4 weeks after discontinuation of antibiotic therapy
*Dual therapy with restrictive labeling - indicated for patients who are either allergic or intolerant to clarithromycin or for infections with known or suspected resistance to clarithromycin.

Triple Therapy

Earlier triple therapy regimens used bismuth plus two antibiotics, most commonly metronidazole and either tetracycline or amoxicillin. These therapy regimens had acceptable eradication rates, however, the patient had to administer several pills three to four times a day, which resulted in poor patient compliance. Compliance is crucial to the success of the regimen. Today, triple therapy regimens, including two antibiotics administered twice daily and an antisecretory agent administered daily or twice daily, are currently recommended as first-line therapy because they are less complex and more tolerable than quadruple therapy and more effective than dual therapy.

Proton Pump Inhibitor plus Two Antibiotics. The FDA-approved triple therapy regimens are very similar. Each of them utilizes the same two antibiotics, amoxicillin and clarithromycin, plus a PPI (esomeprazole, lansoprazole, omeprazole, or rabeprazole). Refer to Table 1. These are not complicated regimens and require dosing only twice a day for 1 to 2 weeks depending on the specific regimen. Currently, only the regimen containing the PPI, rabeprazole, carries an indication for a 1-week duration of therapy. Eradication rates for these triple therapy regimens are high, ranging from 84-92%.^{15, 16} Lansoprazole was the first proton pump inhibitor approved by the FDA for triple therapy; however, esomeprazole, omeprazole, and rabeprazole show similar results in ulcer healing, symptom control, and improving antibiotic effectiveness.

Recent studies have investigated the use of a fluoroquinolone antibiotic instead of clarithromycin with amoxicillin and a proton pump inhibitor. In the United States resistance to clarithromycin has been estimated to be 10.1% nationwide and may be higher in some parts of the country.¹⁷ Resistance rates will continue to rise with increasing usage of clarithromycin and this will negatively affect eradication rates. It is recommended that clarithromycin-containing regimens should be avoided in patients with prior exposure to the drug. During the 68th annual scientific meeting of the American College of Gastroenterology, the results of an intent-to-treat analysis suggested that a fluoroquinolone antibiotic, specifically gatifloxacin, may be a useful alternative treatment for *H. pylori*. Gatifloxacin, it was reported, may be a treatment option in cases of clarithromycin treatment failure. The regimen studied required patients to receive 7 days of gatifloxacin 400mg once daily, plus amoxicillin 1000mg twice daily, plus rabeprazole 20mg twice daily, which resulted in *H. pylori* eradication for 92% of patients enrolled.¹⁸

Quadruple Therapy

Quadruple therapy consists of the traditional BMT regimen (bismuth, metronidazole, and tetracycline) plus an antisecretory agent such as a histamine2-receptor-antagonist (H2RA). This regimen requires the patient receive Bismuth subsalicylate (Pepto Bismol®) 525 mg QID, plus metronidazole 250 mg QID, plus tetracycline 500 mg QID for two weeks, plus the antisecretory agent during the two weeks of antibiotic therapy and two weeks after antibiotics are discontinued. This could be considered the most complex regimen in regards to patient compliance. However, those patients who are treated with this regimen and are compliant do consistently achieve high eradication rates.

The addition of the antisecretory agent to the traditional BMT triple therapy has been shown to improve eradication rates from 83% with the BMT regimen alone to 90% with the addition of omeprazole in a 7-day trial.¹⁹ The quadruple therapy regimen approved by the FDA does not recommend the use of a PPI. However, it is of interest to note that certain studies have indicated that PPI usage is superior to H2RA usage in improving eradication efficacy. One trial compared patients who received a 12-day course of BMT therapy with either omeprazole (20mg BID) or famotidine (40mg at bedtime). The results revealed a 97.6% eradication rate in the omeprazole group compared to 89% in the famotidine group.²⁰ In this same study, patients in the omeprazole group has a higher pretreatment prevalence of metronidazole-resistant strains at 24% compared to the famotidine group at 21%.²⁰

Factors That Affect *H. pylori* Eradication Rate

Three factors can significantly affect cure rates for all of the approved regimens. These include patient compliance, duration of therapy, and antimicrobial resistance.

Patient Compliance. Compliance is essential to the success of any *H. pylori* treatment regimen. It has been shown that patients prescribed bismuth-based combination therapy who took more than 60% of their medication resulted in a cure rate of 96% but only 69% for those who took less than 60%.²¹ Patients must be strongly advised and encouraged to comply with the full treatment regimen in order to maximize the chance for a cure. It is important to use language patients can understand because patients comply better if they understand their treatment and consequences of incomplete treatment. Patients may be motivated by the suggestion that adhering completely to the prescribed regimen for only 2 weeks, even tolerating possible side effects can provide permanent relief of ulcer symptoms. Currently there are two antimicrobial combinations available in easy to use dose packs that may further enhance compliance. Prevpac® consists of lansoprazole, clarithromycin, and amoxicillin to be taken twice a day for 2 weeks. Helidac® consists of bismuth subsalicylate, metronidazole, and tetracycline to be taken four times a day for 2 weeks with an antisecretory agent.

Duration of Therapy. The duration of therapy time span for the FDA-approved treatment regimens indicated for *H. pylori* eradication is dependent upon the specific regimen selected. Currently, the various FDA-approved treatment regimens carry indications with a 7-day, 10-day, or 14-day duration of therapy. Refer to Table 1. Inferior eradication rates can be expected when the treatment regimen is taken for a shorter period of time than the indicated duration of therapy. Patients who adhere to their treatment regimen, including the appropriate duration of therapy, will have a higher potential for *H. pylori* eradication and experience fewer treatment failures.

Antimicrobial Resistance. *H. pylori* resistance to antibiotics is a common cause for treatment failure especially in compliant patients. The presence of pretreatment resistance should be considered in the selection of a treatment regimen and to determine if susceptibility testing is necessary. Resistant strains to metronidazole and clarithromycin are commonly encountered but resistance to amoxicillin and tetracycline is rare. The SHARP study published in 2002 reported an overall resistance in the United States to metronidazole of 36.9%, clarithromycin of 10.1%, and amoxicillin of 1.4%.¹⁷

Pretreatment resistance to metronidazole is most common and thought to be attributed to longer use of the drug and its availability in some parts of the world without a prescription.²² The effect of metronidazole resistance has been found to be variable. There are studies that report a reduction in eradication rates due to metronidazole resistance and other studies that provide evidence that regimens containing metronidazole maintain effectiveness despite the presence of metronidazole resistance.²³

Resistance to clarithromycin is considered a much greater problem. Any clarithromycin-containing regimen will have significant reduction in eradication rate if used in the presence of resistant strains. The growing problem of clarithromycin resistance is a result of increased use of clarithromycin and other macrolides. Cross-resistance among macrolides such as erythromycin has been identified.²² Exposure to clarithromycin without eradication of *H. pylori* has been shown to result in clarithromycin-resistant isolates in two thirds of those treatment failures.²⁴ Therefore, in patients with prior exposure to clarithromycin, an alternative antibiotic regimen should be considered.

Antimicrobial resistance to amoxicillin and tetracycline is rare. These antibiotics can therefore be considered for reuse in cases of treatment failure. In addition to these two antibiotics, bismuth subsalicylate and bismuth citrate have not been linked to the development of resistance.

Part II. *H. pylori* Treatment Among Louisiana Medicaid Recipients

This retrospective analysis of Louisiana Medicaid claims examines treatment alternatives used among recipients with an *H. pylori* infection diagnosis.

METHODS: Paid claims data from January 1998 through December 2002 for recipients with *H. pylori* infection. Recipients were included in the study group if they:

- had at least one claim with a primary or secondary diagnosis of *H. pylori* infection (ICD-9-CM 041.86);
- were eligible for Medicaid benefits every month beginning with the month of their *H. pylori* diagnosis until the end of the study period;
- and were not simultaneously eligible for Medicare benefits.

Treatment alternatives and medication utilization were ascertained from the recipients' pharmacy claims within 6 months of their *H. pylori* diagnosis. NDC codes were used to identify medications indicated for the treatment of *H. pylori* infection. Over-the-counter medications were not investigated since Medicaid does not cover them. The following medications were considered:

- Antibiotics: clarythromycin, amoxicillin, metronidazole, tetracycline, amoxicillin/clavulanate
- Proton Pump Inhibitors (PPI's): omeprazole, lansoprazole, esomeprazole, rabeprazole, pantoprazole
- H2-Receptor Antagonists (H2A's): ranitidine, cimetidine, famotidine, nizatidine
- Combo Packs: Prevpac®, Helidac®

Recipients were considered to have filled a combination therapy if they simultaneously filled prescriptions for both antibiotics and PPIs/H2As, or if they received a combo pack. Recipients without a combination therapy were further investigated for the use of PPIs /H2As alone. The remaining recipients were then examined for the utilization of antibiotics.

Table 2: Utilization of Combination Therapies

	Number of Recipients	Combination Therapies Found in Claims
Combo Packs	279	Prevpac® (clarithromycin + amoxicillin + lansoprazole)
	38	Helidac® (metronidazole + tetracycline + bismuth subsalicylate)
Quadruple Therapies	5	various non-FDA approved therapies
Triple Therapies	96	amoxicillin + clarithromycin + PPI
	19	tetracycline + metronidazole + PPI (<i>to be FDA-approved this regimen must include bismuth*</i>)
	73	various non-FDA approved therapies
Dual Therapies**	15	clarithromycin + PPI
	13	amoxicillin + PPI
	18	various non-FDA approved therapies
Total	556	

* Bismuth cannot be traced in claims, as it is OTC.

**Consider eradication rates.

As with any claims data analysis, information is only available for medical services/drugs for which a paid claim exists, i.e., there is no record of any samples, over-the-counter medications that a recipient may have received, nor prescriptions written but not filled.

RESULTS: For the study period, 1,153 recipients met the inclusion criteria. Of these recipients, 153 did not fill any prescriptions indicated for the treatment of *H. pylori*. The number of recipients who utilized combination therapies and the treatment alternatives used are presented in Table 2. Table 3 shows the number of recipients who filled prescriptions for PPIs and/or H2As only, and the number of prescriptions each recipient filled within 6 months of their *H. pylori* diagnosis. The remaining 251 recipients received antibiotic prescriptions only.

Table 3: Utilization of PPIs and H2As within 6 Months of an *H. pylori* Diagnosis

	Number of Recipients	Number of PPI/H2A Prescriptions per Recipient
	1	12
	1	10
	1	9
	5	7
	15	6
	20	5
	15	4
	30	3
	33	2
	72	1
Total	193	

Table 4: Summary of Results

Recipients	Treated	
153 of 1,153		13.3% of recipients with a diagnosis of <i>H. pylori</i> infection had no prescription for an agent indicated for the treatment of the infection
	251 of 1,000	25.1% of those treated were treated with only an antibiotic
	193 of 1,000	19.3% of those treated were treated with only an H ₂ A or PPI
	556 of 1,000	55.6% of those treated were treated with a combination therapy
317 of 1,153	317 of 1,000	27.5% of recipients diagnosed with <i>H. pylori</i> (31.7% of those who received any drug therapy) received a prescription for a combo pack.
5 of 1,153	5 of 1,000	0.4% of those diagnosed were treated with quadruple therapy (Equates to 0.5% of those with any drug therapy)
	460 of 556	Of the 556 recipients who were treated using a combination therapy, 460, or 82.7%, received an FDA approved therapy.

Conclusion

This brochure has presented therapy alternatives in the treatment of *H. pylori* infections. For completeness, dual therapies were discussed; however, it is important to take into account the efficacy of the current dual therapies when considering treatment options. There are FDA approved triple and quadruple therapies that have been shown to have superior eradication rates in clinical studies. Table 1 presented a summary of the FDA approved therapies.

The analysis of the pharmacy claims suggests that, for this study period, after diagnosis, many recipients did not receive a therapy paid by Medicaid that had been shown to be highly effective in eradication of *H. pylori*. From the claims data, fewer than half (48.22%) appeared to have been treated with a combination therapy. Whether this is because of use of samples, failure to fill prescriptions or because a recipient may already have a prescription for one of the drugs used in combination therapy cannot be determined by the paid claims.

The Louisiana Medicaid program appreciates your service to Medicaid recipients in the state. We hope that the previous brochure that discussed options for testing for *H. pylori* and this brochure that discussed treatment regimens have provided you with information, in an abbreviated format, that will be useful as you care for Louisiana's Medicaid recipients.

References

References available upon request.

Please contact:

Michelle Massey
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Email: mmassey@ulm.edu

Complete Wellness: A Guide to Managing Your Health

* The following is an abbreviated version of the education material sent to selected Medicaid recipients.

Helicobacter Pylori

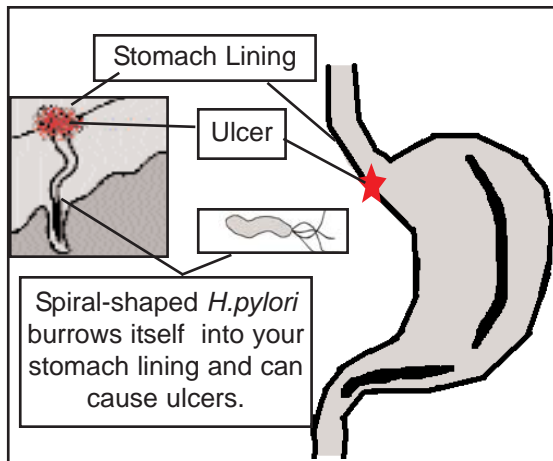
By: Michelle Massey; Sandra G. Blake, PhD; and Catherine L. Whipple, RPh.
The University of Louisiana at Monroe School of Pharmacy

Do you have a peptic ulcer or ulcer symptoms?

If the answer is “yes,” please read this brochure. You could have a bacterial infection called *helicobacter pylori* or *H.pylori*.

What is *H. pylori*?

H.pylori is a spiral-shaped bacterium that burrows itself into the sensitive lining of the stomach. It releases an ammonia-like substance that causes irritation and inflammation, ulcers, and possibly even stomach cancer. Research shows that more than 90% of all gastritis and peptic ulcers are caused by *H.pylori*.



What is a peptic ulcer?

A **peptic ulcer** is a sore in the lining of the stomach. It may also be called a duodenal or gastric ulcer.

How do I know if I have a peptic ulcer?

MOST COMMON SYMPTOMS INCLUDE:

- Burning pain or dull gnawing ache in your stomach or abdomen that usually comes and goes for a few days or weeks.
- Pain usually occurs 2-3 hours after a meal, or in the middle of the night when your stomach is empty.
- Pain can usually be temporarily relieved by eating a meal or taking antacids.



MORE SERIOUS SYMPTOMS:

- Feel sick to your stomach or vomiting.
- Don't feel like eating, or have pain when you eat.
- Have bloating or weight loss.

EMERGENCY SYMPTOMS:

- Vomit that looks like coffee grounds or is bloody.
- Black or bloody stool, or stool that looks like tar.
- Sudden or sharp pain in your stomach.

If you have any of these emergency symptoms you should contact your doctor immediately.

What should I do if I have been diagnosed with a peptic ulcer or, if I have ulcer symptoms?

If you are already being treated for an ulcer, ask your doctor about being tested for *H.pylori*. If you have ulcer symptoms and you are not being treated, you should contact your doctor.

Educational material provided to Louisiana Medicaid recipients and providers by the Louisiana Medicaid Pharmacy Benefits Management Program (PBM) in the Department of Health and Hospitals and developed by the University of Louisiana at Monroe School of Pharmacy.

Ask your doctor, pharmacist, or nurse about the information contained in this brochure.

How will my doctor know if I have the *H. pylori* bacterium?

If you have not previously been diagnosed with an ulcer, your doctor may perform an endoscopy. This is where a thin lighted tube with a flexible video camera is inserted down your throat and into your stomach. This allows your doctor to look at and take pictures of the inside of your stomach to see if you have an ulcer.

Once your doctor knows that you have an ulcer, the next step is to find out what is causing the ulcer. It is important to know what is causing your ulcer because the treatments are different.

There are four tests that your doctor may use to check for *H.pylori*. These tests are:

1. Blood Test
2. Breath Test
3. Stool Sample
4. Tissue Test

Is there any way to treat *H. pylori*?

H.pylori was not discovered until the 1980s. Before its discovery, doctors were treating all peptic ulcers with the same medications; however, when *H.pylori* was present, these drugs would relieve the pain for a while, but the ulcers would almost always come back.

Now that doctors know most peptic ulcers are caused by *H.pylori*, they are able to treat your ulcer **and** prevent it from returning.

If you have an ulcer caused by *H.pylori* your doctor may prescribe an anti-ulcer drug, but it will probably be taken with other drugs as part of a triple therapy.

Your doctor may prescribe:

- * A medication to stop your stomach from producing acids,
- * An antibiotic to kill the *H.pylori* bacteria, and
- * An antacid to protect your stomach from the acids and reduce the pain.

NOTE: Take all of your medication. If you stop taking your medication too soon the *H.pylori* may still be there and your ulcer will come back.

You will probably have to take several pills each day for several weeks to get rid of the *H.pylori*. You may also experience some mild side effects from the medications, such as nausea, dizziness, diarrhea, or headaches. It has been proven that taking these medications together is the best way to kill the *H.pylori* and permanently cure your ulcer.

How can I protect myself from *H. pylori*?

Nobody knows for sure how *H.pylori* spreads, so nobody knows how to prevent getting it. *H.pylori* may be spread through contaminated food or water, or even through saliva or fecal matter, but this is not known for sure.

If I have *H. pylori*, is there anything I can do to prevent ulcers or keep them from getting worse?

If your doctor tells you that you have *H.pylori* or peptic ulcers, here's what you can do to keep them from getting worse:

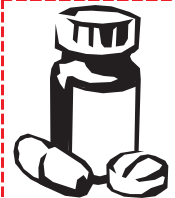
Don't Smoke



Avoid Alcohol



Talk to your doctor about any medications that you take, including aspirin and other over-the-counter drugs.



Ulcer Facts

- ♦ Spicy foods and stress DO NOT cause ulcers.
- ♦ One in ten Americans develops an ulcer at some point during his/her life.
- ♦ *H.pylori* causes more than 90% of all duodenal ulcers and up to 80% of gastric ulcers.
- ♦ Not all people who have *H.pylori* develop ulcers.

For More Information Please Contact:

National Digestive Diseases Information Clearinghouse

2 Information Way
Bethesda, MD 20892-3570
Phone: 1-800-891-5389
Email: nddic@info.niddk.nih.gov

Centers for Disease Control and Prevention National Center for Infectious Diseases

1600 Clifton Road, MS-A49
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Complete Wellness:
A Guide to Disease Management